Routine surgery in addition to chemotherapy for treating spinal tuberculosis

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Published in:
Cochrane Database of Systematic Reviews

DOI:
10.1002/14651858.CD004532.pub2

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Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD004532.
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[Intervention Review]

Routine surgery in addition to chemotherapy for treating spinal tuberculosis

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Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 5, 2013.

Citation: Jutte PC, van Loenhout-Rooyackers JH. Routine surgery in addition to chemotherapy for treating spinal tuberculosis. *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No.: CD004532. DOI: 10.1002/14651858.CD004532.pub2.

ABSTRACT

Background

Tuberculosis is generally curable with chemotherapy, but there is controversy in the literature about the need for surgical intervention in the one to two per cent of people with tuberculosis of the spine.

Objectives

To compare chemotherapy plus surgery with chemotherapy alone for treating people diagnosed with active tuberculosis of the spine.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register (February 2010), CENTRAL (*The Cochrane Library* 2010, Issue 1), MEDLINE (1966 to February 2010), EMBASE (1974 to February 2010), LILACS (1982 to February 2010), conference proceedings, and reference lists. A search update in November 2012 revealed no new studies.

Selection criteria

Randomized controlled trials with at least one year follow up that compared chemotherapy plus surgery with chemotherapy alone for treating active tuberculosis of the thoracic and/or lumbar spine.

Data collection and analysis

Two authors independently assessed trial eligibility, methodological quality, and extracted data. We analysed data using odds ratio with 95% confidence intervals.

Main results

Two randomized controlled trials (331 participants) met the inclusion criteria. They were conducted in the 1970s and 1980s with follow-up reports available after 18 months, three years, and five years; one trial also reported 10 years follow up. Completeness of follow up varied at the different time points, with less than 80% of participants available for analysis at several time points. There was no statistically significant difference for any of the outcome measures: kyphosis angle, neurological deficit (none went on to develop this), bony fusion, absence of spinal tuberculosis, death from any cause, activity level regained, change of allocated treatment, or bone loss. Neither trial reported on pain. Of the 130 participants allocated to chemotherapy only, 12 had a neurological deficit and five needed a decompression operation. One trial suggested that an initial kyphosis angle greater than 30° is likely to deteriorate, especially in children.

Authors' conclusions

The two included trials had too few participants to be able to say whether routine surgery might help. Although current medication and operative techniques are now far more advanced, these results indicate that routine surgery cannot be recommended unless within the context of a large, well-conducted randomized controlled trial. Clinicians may judge that surgery may be clinically indicated in some groups of patients. Future studies need to address these topics as well as the patient's view of their disease and treatment.

PLAIN LANGUAGE SUMMARY

Not enough evidence on the routine use of surgery in addition to drug treatment for people with tuberculosis of the spine

Spinal tuberculosis (spinal TB) occurs in about 1% to 2% of people with TB (the most common infectious disease in the world). The disease can have a major impact on people's lives. Nerves can be squeezed causing pain, loss of feeling, and breathing problems. It can cause bone loss and curvature of the spine, which can lead to loss of nerve function and paralysis after some years, even if the TB has been cured. Correcting with surgery at this point can be difficult because of the complexity of the surgery required. It has been suggested that surgery might be undertaken at the time the TB of the spine is diagnosed and drug treatment (chemotherapy) is being used. However, all surgery has potential adverse effects. This review of trials found there were insufficient numbers of participants in the two trials located (331 participants) to be able to say if routine surgery early on was of overall benefit. Further trials are needed and such trials should assess the pain that people suffer and their views of the disease and treatment.

BACKGROUND

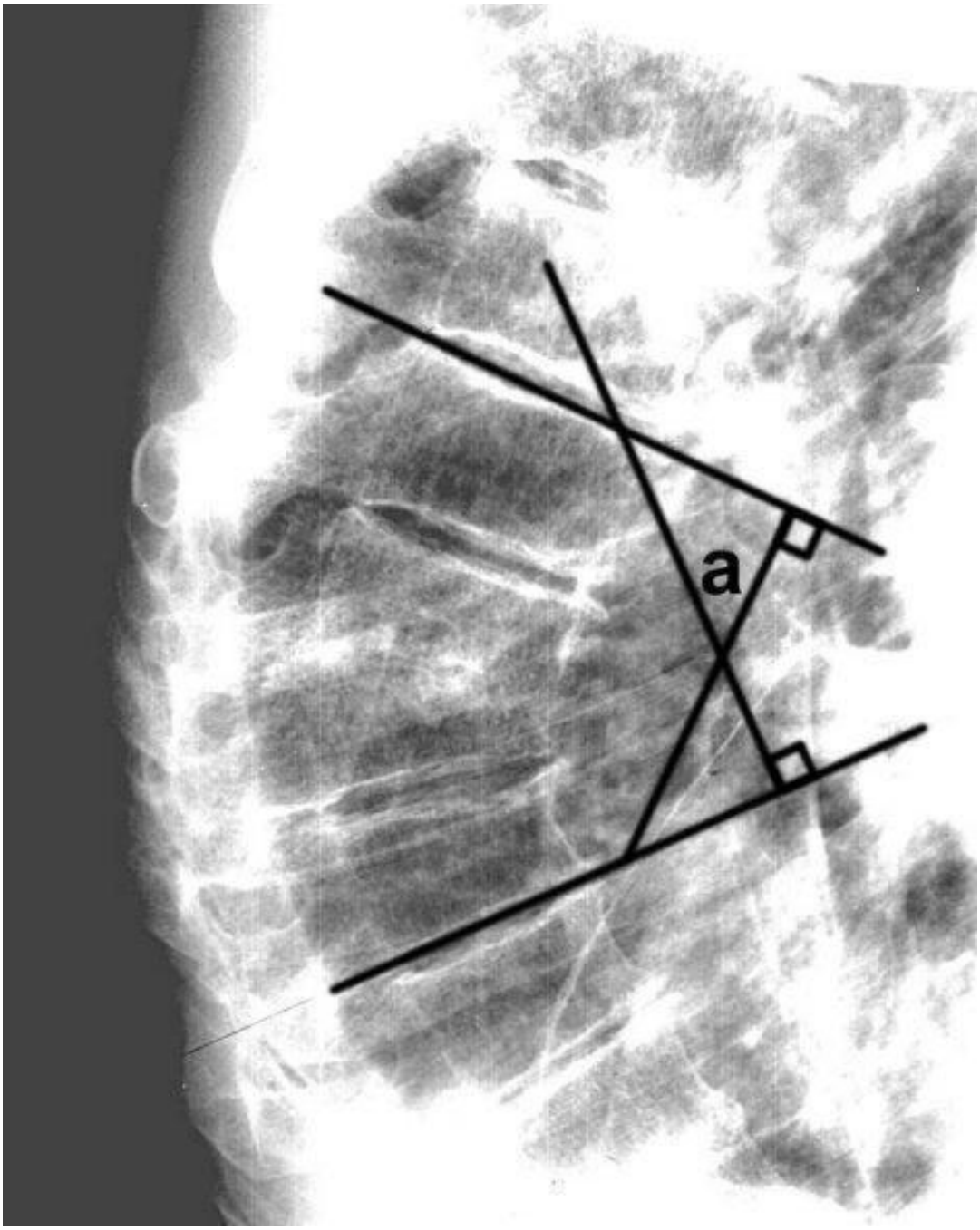
Incidence

Tuberculosis is the most common infectious disease in the world. Every year 10 million new people are infected (WHO 2005). While tuberculosis commonly infects the lungs, it is located in the spine in one to two per cent of people (Watts 1996).

Pathology

Tuberculosis of the spine is potentially serious. The infection can cause pain and destroy the bone making the vertebral bodies collapse, thereby flexing the spine forward (kyphosis) (Figure 1). Sometimes a nerve root may be compressed causing pain along the root or deficit, but more commonly spinal cord compression may lead to myelopathy (loss of feeling and muscle control) or paraplegia. Even lung function may be compromised (Smith 1996). If there is a sharp angle in the spine due to bony destruction, loss of neurological function may manifest only after years, even if the tuberculosis has been cured adequately (Hsu 1988; Rajeswari 1997a; Luk 1999). This is the result of chronic compression of the spinal cord or a local reactivation. Late paraplegia due to spinal cord compression is a major problem because an operation at this stage is complex and prone to major complications often without subsidence of the neurological deficit (Moon 1997). If the bone has fully fused in a normal position after the primary illness period, this late consequence is thought not to occur (Leong 1993).

Figure 1. Lateral radiograph of the spine shows a kyphosis angle because two vertebral bodies were destroyed by tuberculosis; the bodies have fused, and further deterioration of the angle is unlikely. The angle is measured by drawing lines parallel to the healthy vertebral bodies above and below the fused bodies



Most experts believe that a kyphosis over 30° is likely to generate back pain and to deteriorate (Kaplan 1952; Rajeswari 1997b; Wimmer 1997; Parthasarathy 1999 (*see* ICMR/MRC 1989)). Vertebral body bone loss is a measure of destruction of the bone as seen on lateral radiographs. It is expressed as units (U), 1.0 U meaning a complete vertebral body and 0.0 U meaning no bone loss; for example, if two bodies are partially destroyed, one lost 50% of its volume and the other 25%, the bone loss is 0.75 U. It has been claimed to predict the final kyphosis angle (Rajasekaran 1987).

Diagnosis

Diagnosis of spinal tuberculosis in endemic areas is made mainly using radiographs. Active disease is diagnosed when there is loss of the thin cortical outline and rarefaction of the affected vertebral bodies (MRC 1974a). Ideally there is a positive culture from the site of the lesion.

Treatment

Tuberculosis in general is curable. The mainstay of treatment is chemotherapy with at least isoniazid, rifampicin, and pyrazinamide. The American Thoracic Society recommends six months of chemotherapy for spinal tuberculosis in adults and 12 months in children because reliable data are lacking on shorter treatment duration (Bass 1994). The British Thoracic Society recommends six months of treatment irrespective of age (BTS 1998). In their recent review of the literature, Van Loenhout-Rooyackers and colleagues found that six months of treatment is probably sufficient for everyone (Van Loenhout 2002).

Goals of treatment

In tuberculosis, treatment is considered to be successful when the person is cured, is no longer infectious, and does not suffer relapse. However, some additional unique problems are encountered in spinal tuberculosis, namely, kyphosis angle and neurological deficit. Treatment in spinal tuberculosis is directed toward controlling or correcting the kyphosis angle thereby restoring the balance of the spine, restoring normal neurology, preventing pain, achieving early bony fusion (healing), preventing local recurrence of spinal tuberculosis, and preventing bone loss. Furthermore, people need to regain their previous activity level to enable them to resume their normal lives, school, jobs, and sports.

Human immunodeficiency virus (HIV) increases the risk of reactivation of a latent focus and progression of the disease to a more atypical and severe course. Studies directed specifically at spinal tuberculosis and HIV conclude that good clinical outcomes can be expected irrespective of the HIV status and the availability of antiretroviral therapy (Leibert 1996; Govender 2000). Another report mentions that people with HIV are not a homogeneous group, and that results — especially complications like wound infections — worsen during the end stage of the disease (Jellis 1996).

Role of surgery

There is controversy in the literature about the necessity of additional surgical intervention to spinal tuberculosis treatments. This difference of opinion goes back to 1960 when Hodgson and Stock advocated surgical treatment (Hodgson 1960), and Konstam and colleagues advocated conservative treatment (Konstam 1958; Konstam 1962). Conservative treatment consists of only medication and sometimes additional non-operative measures (physical therapy, orthosis, and bed rest). Surgery can basically be divided into two procedures. The first is a debridement. This is a procedure that comprises surgical removal of the infected material. No attempt is made at stabilizing the spine. The second form, which is more extensive, is a debridement with stabilization of the spine (spinal reconstruction). The reconstruction has always been performed with bone grafts. Today, countries with sufficient resources perform stabilization using artificial materials like steel, carbon fibre, or titanium (instrumentation).

Although randomized controlled trials investigating indications are lacking, many authors consider the following indications for surgical intervention: (1) neurological deficits (with an acute or non-acute onset) caused by compression of the spinal cord; (2) spinal instability caused by destruction or collapse of the vertebrae, destruction of two or more vertebrae, or kyphosis of more than 30°; (3) no response to chemotherapeutic treatment; (4) non-diagnostic biopsy; and (5) large paraspinal abscesses (Vidyasagar 1994; Chen 1995; Nussbaum 1995; Rezai 1995; Boachie-Adjei 1996; Watts 1996; Moon 1997). Some authors even advocate surgery in mild cases of spinal tuberculosis (Leong 1993; Luk 1999; Turgut 2001).

Potential benefits of surgery are less kyphosis, immediate relief of compressed neural tissue, quicker relief of pain, a higher percentage of bony fusion, quicker bony fusion, less relapse, earlier return to previous activities, and less bone loss. It may also prevent late neurological problems due to kyphosis of the spine if fusion has not occurred (Hsu 1988; Leong 1993).

Surgery requires expertise, good anaesthesia, and excellent perioperative care. It also requires hospitalization, and is expensive and potentially dangerous. Complications can occur during the operation or postoperatively. Complications of spinal surgery can be divided into several groups: reconstruction-related, vascular, neurological, visceral, and wound-related. Reconstruction failures can be breakage of the graft, screws and rods, loss of correction, and failure of fusion (Jutte 2002). Vascular problems during surgery can be massive bleeding, haematoma formation, and thromboem-

bolism. Neurological damage of surgery can be nerve root lesion, dura tears, spinal cord infarction, and plexus lesions. Visceral damage, especially ureteric lesions, can occur. Wound infections happen in 1% to 6% of spinal surgeries (Fardon 2002). Considering the potential complication rate, surgery should only be performed if there is a clear benefit.

OBJECTIVES

To compare chemotherapy plus surgery with chemotherapy alone for treating people diagnosed with active tuberculosis of the spine.

METHODS

Criteria for considering studies for this review

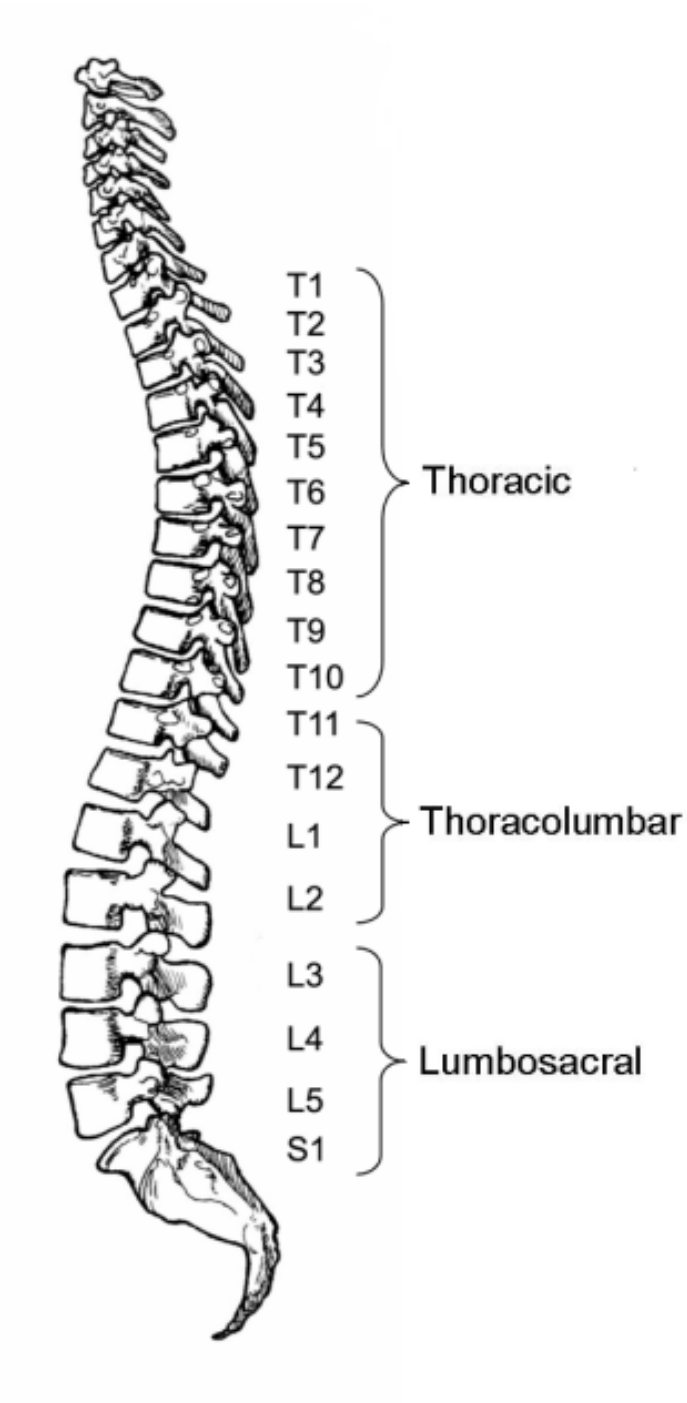
Types of studies

Randomized controlled trials with at least one year follow up after the start of treatment.

Types of participants

People diagnosed with active tuberculosis of the thoracic and/or lumbar spine, including the upper sacral vertebra S1 (Figure 2).

Figure 2. Lateral drawing of the spine illustrating the various levels



Active disease is diagnosed on the radiographs; there is loss of the thin cortical outline and rarefaction of the affected vertebral bodies (MRC 1973a).

Types of interventions

Intervention

Chemotherapy plus surgery.

Control

Chemotherapy.
Both the intervention and control group must have received comparable adequate chemotherapy regimen of at least six months. Adequate refers to the guidelines commonly used when the trial took place.

Types of outcome measures

We assessed all outcome parameters reported at any follow-up time.

Primary

- Kyphosis angle.
- Neurological deficit.

Secondary

- Pain.
- Bony fusion, defined as the healing of adjacent affected vertebral bodies. There is continuity of trabeculae (bone bars) between the vertebral bodies and/or stout bony bridges, usually best seen in the anteroposterior radiograph, projecting up to 2 cm wide of the vertebral bodies and showing trabecular continuity even though the vertebrae are still separated by a small space, often no more than a hairline.
- Absence of spinal tuberculosis.
- Deaths from any cause.
- Regained activity level, defined as the number of participants that regained their previous activity level, which is the ability of people to resume their normal lives, do their previous jobs, sports, etc.
- Bone loss, defined as a measure of destruction of the bone as seen on lateral radiographs. It is expressed as units (U), 1.0 U being loss of a complete vertebral body and 0.0 U being no bone loss; for example, if two bodies are partially destroyed, one lost 50% of its volume and the other 25%, the bone loss is 0.75 U.

Adverse events

Events related or probably related to the treatment having a negative effect on the well-being of the participants other than death (reported separately); this includes surgical complications, failure of reconstruction, paraplegia from the operation, and adverse effects of medication.

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Databases

We searched the following databases using the search terms and strategy described in Appendix 1. Cochrane Infectious Diseases Group Specialized Register (February 2010); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2010, Issue 1); MEDLINE (1966 to February 2010); EMBASE (1974 to February 2010); LILACS (1982 to February 2010). A search update was conducted on 28 November 2012.

Reference lists

We also checked the reference lists of all studies identified by the above methods.

Data collection and analysis

Selection of studies

We scanned the results of the literature search for potentially relevant trials and retrieved their full articles. We independently assessed the potentially relevant trials for inclusion in the review using an eligibility form based on the inclusion criteria. We ensured each trial was included only once and resolved disagreements through discussion. The excluded studies are listed together with the reason for excluding them in the 'Characteristics of excluded studies'.

Data extraction and management

The first author extracted the data using a data extraction form and entered the data into Review Manager 5. The second author cross checked the data with the original paper. We also extracted

the number of participants allocated to surgery who were not operated on, and those allocated to chemotherapy alone who received surgery. We resolved disagreements by referring to the original paper.

Data on neurology, pain, bony fusion, absence of spinal tuberculosis, death from any cause, activity level, and change of allocated treatment were handled as dichotomous data. Data on angle of kyphosis can be handled as continuous or dichotomous. Continuous was preferred, but the required data on standard deviation were not provided. We handled the data as dichotomous data in two ways: (a) a final kyphosis angle being $\leq 30°$ or $> 30°$; and (b) a progression $\leq 10°$ or $> 10°$.

Assessment of risk of bias in included studies

We independently assessed the methods used to generate the allocation sequence and conceal allocation as adequate, inadequate, or unclear according to Jüni 2001. We also assessed the inclusion of all randomized participants in the final analysis and considered at least 80% completeness of follow up at each time point to be adequate. Blinding of the treating physicians was not possible at the time of treatment or at follow up. Blinding of the assessor of the radiographs of both trials was limited to pre-treatment investigations. At follow up, no information of the treatment given was provided; signs can frequently be seen on radiographs after an operation, especially after a reconstruction with a bone graft. We resolved any disagreements through discussion.

Data synthesis

We analysed the data using Review Manager 5. We used odds ratio (OR) to assess all dichotomous outcome measures. We used the fixed-effect model and presented the data with 95% confidence intervals (CI).

RESULTS

Description of studies

Search results

The search strategy revealed 25 potentially relevant papers; their reference lists revealed another three. We studied the full-text versions of all 28 papers. We excluded 21 papers (*see* 'Characteristics of excluded studies') and included seven publications reporting on two randomized controlled trials involving 331 participants (*see* 'Characteristics of included studies').

The British Medical Research Council Working Party on Tuberculosis of the Spine (MRC) co-ordinated both randomized controlled trials, one in co-operation with the Indian Council of Medical Research (ICMR). The MRC performed a series of randomized controlled trials investigating the varying ways of treatment of tuberculosis of the spine in several centres. This review includes two of these trials: one from Bulawayo, Rhodesia (now Zimbabwe) (MRC 1974a); and the other from Madras, India (ICMR/MRC 1989).

The different publications reported on the trials after 18 months, three years, and five years (MRC 1974a; ICMR/MRC 1989); ICMR/MRC 1989 also reported 10 years follow up. The results at five years for ICMR/MRC 1989 were described in three different papers. We used an article published by the MRC in 1999 to assess the five year follow up of ICMR/MRC 1989 as it is the official report of the trial and provides the most detailed information of all three.

Participants

We have detailed the inclusion and exclusion criteria in the 'Characteristics of included studies' and summarized the characteristics of the 331 enrolled and randomized participants in Appendix 2. Trials reported on the number of participants evaluable at the various times of follow up (Figure 3 and Figure 4). Both trials included children (less than 15 years old) and adults, men and women. The location of the spinal lesion was thoracic (T1 to T10), thoracolumbar (T11 to L2), and/or lumbosacral (L2 to S1) (Figure 2). A few participants had neurological deficit on entry but all were able to walk.

Figure 3. Participant flow in MRC 1974a

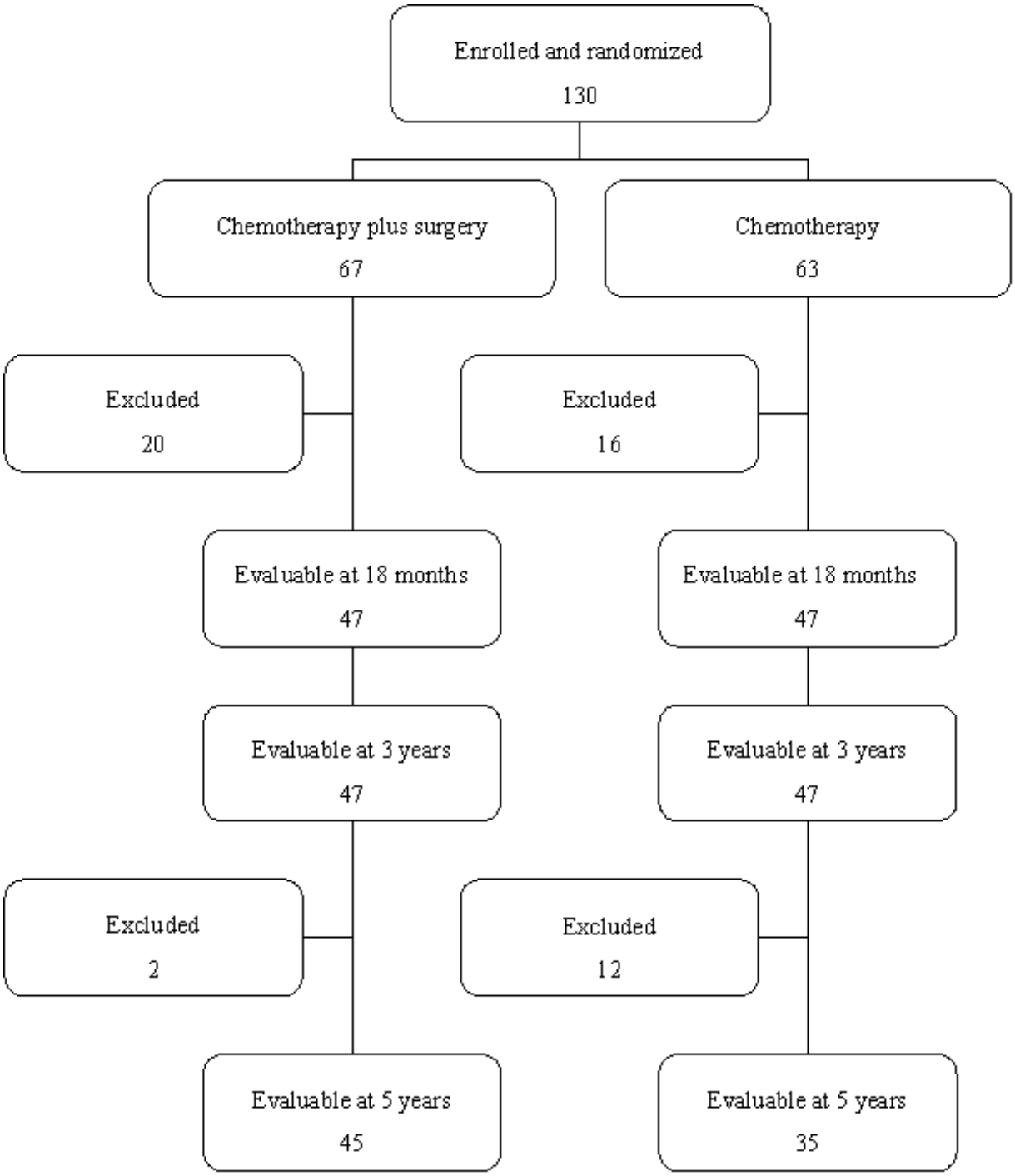
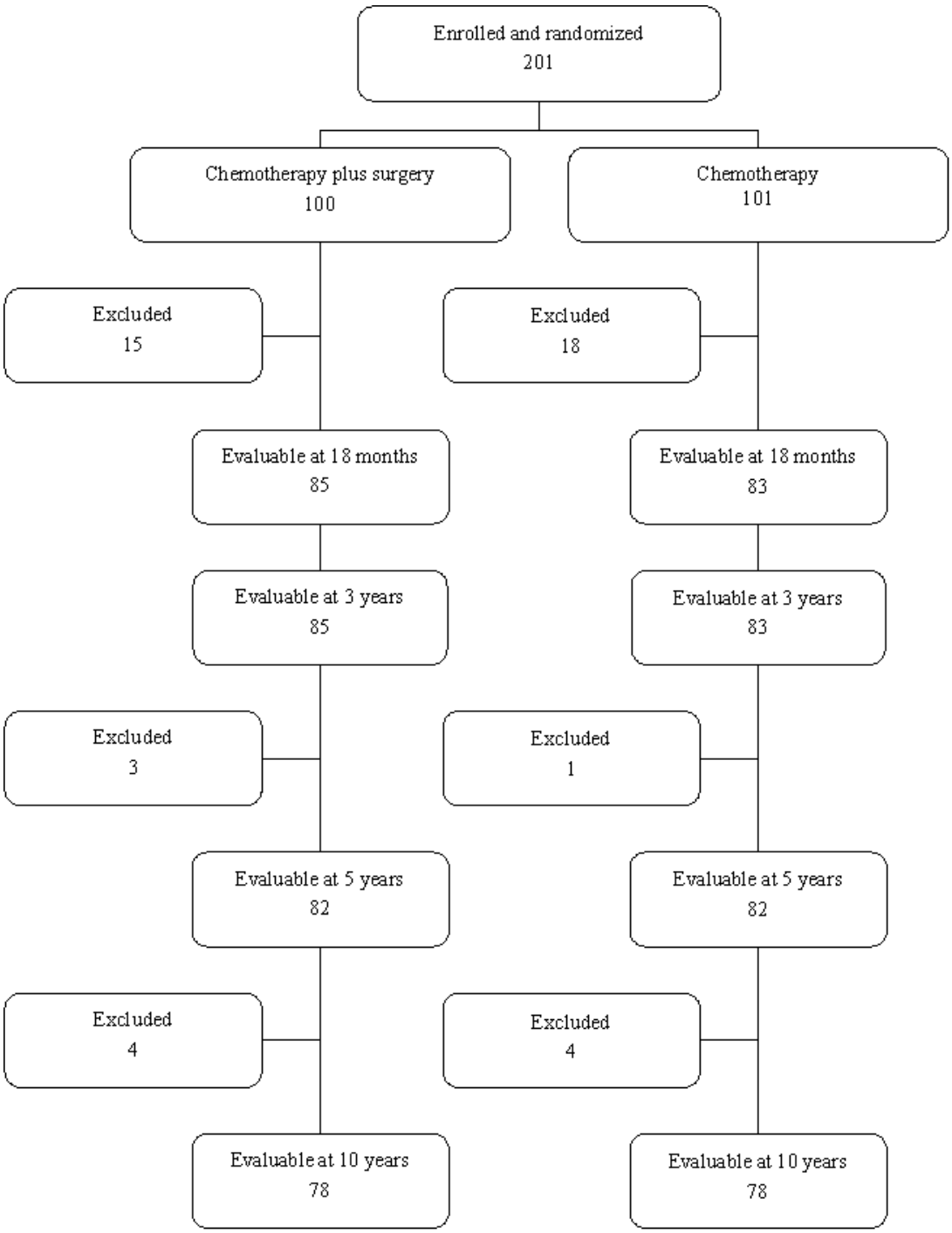


Figure 4. Participant flow in ICMR/MRC 1989



Interventions

MRC 1974a randomized 130 people to chemotherapy plus surgical debridement (no reconstruction) or chemotherapy alone. All participants received p-amino salicylic acid (PAS) and isoniazid for 18 months. Half of them were randomized to receive streptomycin as extra in the first three months. We were unable to determine exactly which individual participants received streptomycin, but for the purpose of this review we did not consider this a reason for exclusion. Streptomycin is not a potent drug in the treatment of tuberculosis and is no longer part of the recommended treatment regimen (Bass 1994; BTS 1998).

ICMR/MRC 1989 randomized 201 participants to chemotherapy plus surgery (debridement and reconstruction with bone graft) or to chemotherapy alone. The chemotherapy for all participants was a six-month regimen of isoniazid and rifampicin. The trial also included a third arm, which we had to exclude because these participants received a different chemotherapy regimen consisting of nine months treatment.

Outcomes

The trials reported on all the prespecified outcome measures except pain.

Risk of bias in included studies

See 'Assessment of risk of bias in included studies' *for details and a summary of the quality assessment in* Appendix 3.

The methods used to generate the allocation sequence were unclear in both trials, but the concealment of allocation was adequate. Completeness of follow up in the MRC 1974a trial was inadequate after three years (72%) and five years (62%). In the ICMR/MRC 1989 trial, it was adequate at three years (83%) and five years (82%), but inadequate at 10 years (78%).

Effects of interventions

Analysis in the two trials appeared to be by intention to treat. In the chemotherapy group across the two trials, 12 participants had neurological complications at entry to the trial: five of these required surgery. Details on reasons behind the change of allocated treatment are given in Appendix 4. In the chemotherapy plus surgery group across the two trials, there was a problem with exposure of the bone during operation in two participants and the procedure was abandoned: both were treated with chemotherapy only. We looked for a difference in the numbers of participants where their actual treatment group was different to what they were originally randomized to and detected no difference (Analysis 1.1).

Kyphosis angle

Both trials reported on kyphosis angle. They used two methods to report change in the angle.

Mean increase of kyphosis angle (progression of kyphosis angle at follow up)

Both trials reported that the mean degree of kyphosis angle was within the same range at 18 months, three years, five years, and 10 years (Appendix 5), but we were unable to assess statistical significance because standard deviations were not provided.

In ICMR/MRC 1989 at 10 years follow up, a kyphosis of greater than 30° at the start of treatment deteriorated (increased) with a mean of 10° to 30°. The investigators describe a subgroup effect for age on kyphosis angle for the chemotherapy group: 17 participants younger than 15 years with an initial angle greater than 30° had a mean deterioration of 30° compared with the same treatment in 13 participants older than 15 years with angles greater than 30° who deteriorated with a mean of 10° (P = 0.001).

Kyphosis angle: > 10° deterioration

MRC 1974a measured this at five years (65 participants) for lesions in the thoracic, thoracolumbar, and lumbosacral areas (T1 to S1), and ICMR/MRC 1989 measured this at three years (78 participants) and five years (79 participants) for lesions in the thoracic and thoracolumbar areas (T1 to L2). There was no statistically significant difference between groups at three years (78 participants, 1 trial) or five years (144 participants, 2 trials); Analysis 1.2.

Neurological deficit

Both sets of trials reported on the neurological status of the participants. No participants without neurological deficit on entry developed neurological deficit. Neurological deficit was present at entry in 23 participants and there was no statistically significant difference at 18 months (23 participants, 2 trials), three years (23 participants, 2 trials), five years (20 participants, 2 trials), and 10 years (10 participants, 1 trial); Analysis 1.3.

Pain

Neither trial reported on pain.

Bony fusion

There was no statistically significant difference between chemotherapy plus surgery and chemotherapy alone on the presence of bony fusion at 18 months (256 participants, 2 trials), three years (247 participants, 2 trials), five years (236 participants, 2 trials), or 10 years (156 participants, 1 trial); Analysis 1.4.

Absence of spinal tuberculosis

There was no statistically significant difference between the intervention and control at 18 months (261 participants, 2 trials), three years (262 participants, 2 trials), five years (244 participants, 2 trials), and 10 years (156 participants, 1 trial); Analysis 1.5.

Deaths from any cause

Both sets of trials reported on deaths from any cause (details provided in Appendix 6). There was no statistically significant difference between the groups at 18 months (262 participants, 2 trials) or three years (262 participants, 2 trials); Analysis 1.6. Follow up at five or 10 years was impossible to assess because details on which patient died in which group were not provided.

Regained activity level

Both sets of trials reported on activity level, but neither provided data on the participants' activity levels when they entered the trials. Around 90% of participants in both groups had reached their previous level of activity at 18 months follow up. One of the prerequisites for regaining activity level is normal neurology. There were no statistically significant differences between the groups at 18 months (262 participants, 2 trials), three years (262 participants, 2 trials), five years (244 participants, 2 trials), or 10 years (156 participants, 1 trial); Analysis 1.7.

Bone loss

The trials used two methods of reporting data on bone loss.

Mean change of bone loss (mean difference between loss at entry and at follow up)

Neither trial report included standard deviations, which meant that we were unable to assess the statistical significance of the data on the mean bone losses. The major bone loss (vertebral destruction) was present at the time of diagnosis; only limited further destruction occurred during treatment and the subsequent follow-up period (*see* Appendix 7).

Large change in bone loss

An unwanted result is considered when the amount of bone loss has deteriorated greater than 0.25 U. MRC 1974a reported on this at five years (58 participants), and ICMR/MRC 1989 reported data at three years (161 participants) and five years (150 participants). There was no statistically significant difference at three years (161 participants, 1 trial) or five years (220 participants, 2 trials); Analysis 1.8.

Adverse events

Adverse events were defined as events related or probably related to the treatment having a negative effect on the well-being of the participants other than death (reported separately). Adverse events were not specifically reported by the trial authors, so we analysed the text to identify them (Appendix 8). One participant was operated on the wrong localization, there were seven graft failures (breakage and displacement), and 28 cases of hepatitis, a side effect of the chemotherapy.

DISCUSSION

The objective of this systematic review was to compare chemotherapy plus surgery with chemotherapy alone for treating people diagnosed with active tuberculosis of the thoracic and/or lumbar spine. No statistically significant benefit of routine surgery was found. Most participants received the treatment of the group to which they were allocated. Reasons for changing treatment were mainly neurological: five of 12 participants from the chemotherapy group had surgery because of persisting or deteriorating neurological deficit. Participants with neurological deficit form an interesting subgroup for further studies.

Effects on the spine

The review did not demonstrate an effect of surgery on the kyphosis angle. The incidence of progressive kyphosis was high for all participants, as was the kyphosis angle at the start of either treatment. Many spine surgeons nowadays consider a kyphosis greater than 30° to be unacceptably high and an indication for operative correction in the first place (Vidyasagar 1994; Chen 1995; Nussbaum 1995; Rezai 1995; Boachie-Adjei 1996; Watts 1996; Moon 1997). Nor did the review show a difference with respect to bony fusion, often considered the best evidence of healing (MRC 1974a). Further deterioration of the kyphosis angle is unlikely after fusion. There was no statistically significant difference between the two intervention groups on the presence of bony fusion at any reported follow up. Data on the speed of bony fusion were not provided in either trial, so differences during early phases of treatment could not be assessed. Over time, bony fusion is obtained in a high percentage of participants regardless of the way of treatment. Similarly, bone loss was not influenced by treatment group. The amount of bone is considered important for the stability of the spine. People with a total bone loss of more than three U were excluded, and the role of surgery in these more severe cases could not be assessed.

Neurological deficit and mobility

A small number of participants had a neurological deficit at entry, and there were no statistically significant differences between the interventions in the improvement of this deficit. Deterioration of neurological deficit or persisting deficit with spinal cord compression can be an indication for surgery (Martini 1976; Leong 1993; Watts 1996; Moon 1997). There was a subgroup of 12 participants from the chemotherapy only group (130) with neurological deficit on entry; five of these 12 needed an operation to decompress the spinal cord.

Two studies reporting on non-surgical treatment of spinal tuberculosis conclude that it is successful in the majority of cases, even in the presence of neurological deficit (Pattison 1986; Nene 2005). However, the participants were not randomized, one of the studies was retrospective (Nene 2005), and the follow up was 25% at five years for the other report (Pattison 1986).

Some authors advocate the so-called 'middle path regimen' in which only patients with neurological deficit have operations (Tuli 1975; Jain 2004). They report good results, but there are no trials comparing this regimen to purely non-surgical treatment or routine surgical treatment. None of the participants included in the included trials were paralysed severely enough to prevent them from walking across a room. Therefore the role of surgery in these more severe cases could not be assessed.

Almost all participants reached their previous activity levels at first follow up, regardless of treatment. However, data on activity level on entry of the study were not provided, so the actual improvement could not be assessed. Furthermore, there may have been differences in the speed of recovery. Regrettably neither trial assessed this.

Deaths and adverse events

There was no statistically significant difference in the number of deaths from any cause at 18 months or three years follow up. Because the trials did not provide details, we were unable to assess the mortality at five or 10 years. In ICMR/MRC 1989, four participants died as a consequence of surgical procedures. The procedure was introduced to the orthopaedic centre for this particular trial. Because of these deaths, the investigators concluded that there are problems in introducing a new major surgical procedure, even in an orthopaedic centre, and suggest that in the light of the excellent results achieved by chemotherapy alone that this procedure need not and should not be introduced (ICMR/MRC 1989). The operations with their high mortality rate (4/85) were performed between 1975 and 1978. Perioperative care has improved since, and no deaths have been reported from more recent series of operations (Güven 1994; Rezai 1995; Lee 1999; Turgut 2001; Sundararaj 2003).

Most adverse events were related to surgery. In ICMR/MRC 1989, four people died due to complications related to surgery, some of these are preventable with modern day knowledge. There were several problems related to the bone graft. The same trial reported that three or more disc spaces had to be spanned in seven participants with a kyphosis greater than 30°. All seven bone grafts failed (breakage or displacement) and the deformity progressed. Modern spinal instrumentation might prevent this failure.

There were no participants reported with cardio-respiratory failure related to the deformity. In neither series there were participants with late paraplegia in spite of some severe deformities. Follow up of 10 years might not be sufficient for this late paraplegia; it may only manifest itself after more than 15 years (Seddon 1935; Hsu 1988; Leong 1993; Luk 1999).

Limitations of the review

Follow up was inadequate for MRC 1974a at any time point and for 10 years follow up of ICMR/MRC 1989. In both sets of trials different techniques of surgery were used: debridement surgery (MRC 1974a) and debridement plus reconstruction with bone graft (ICMR/MRC 1989). As shown in the meta-analyses, there were no statistically significant differences between these techniques. Both sets of trials were performed many years ago, between 1964 and 1969 for MRC 1974a and between 1975 and 1978 for ICMR/MRC 1989. In recent years, new medications and better operative techniques have been developed.

The introduction of pyrazinamide in 1978 dropped the relapse rates for pulmonary tuberculosis from 7.8% and 20.3% to 1.4% and 3.4% after two and five years follow up, respectively (MRC 1987). Randomized controlled trials are needed to assess this newer medication in spinal tuberculosis.

Better techniques for correcting deformities of the spine like kyphosis and scoliosis are continually being developed. These techniques using metal or titanium screws, plates, and rods (instrumentation) have reported to be good at maintaining this correction (Güven 1994; Moon 1995; Rajasekaran 1998; Lee 1999; Özdemir 2003; Sundararaj 2003). However, no randomized controlled trials have been performed comparing chemotherapy alone with chemotherapy plus surgical instrumentation, and they are unlikely to be conducted because the main debate in spinal surgery is now whether the instrumentation should be anterior, posterior, or both (Güven 1994; Moon 1995; Moon 1997; Rajasekaran 1998; Özdemir 2003; Sundararaj 2003).

Another limitation of the review is that there were no data on how the patients found their treatment. It would be helpful if future studies also address this point.

AUTHORS' CONCLUSIONS

Implications for practice

Two trials evaluated routine surgery in spinal tuberculosis, but data are insufficient to be clear whether this policy is better than

chemotherapy alone (with surgery used when clinically indicated). These trials were performed some years ago, and current medication and operative techniques are far more advanced. However, these results indicate that routine surgery cannot be recommended unless within the context of a large, well-conducted randomized controlled trial.

Clinicians may judge that surgery may be indicated in subgroups of patients – with an initial kyphosis angle greater than 30° (especially in children) or progressive or persistent neurological deficit with spinal cord compression despite chemotherapy – but there are no randomized comparisons to support this.

Implications for research

Future trials need to assess routine surgery and also address subgroups of patients with spinal tuberculosis to establish the role of surgery for specific indications. These trials need to be large enough to assess outcomes properly. They need to assess pain and the patient's view of their disease and treatment.

ACKNOWLEDGEMENTS

This document is an output from a project funded by the UK Department for International Development (DFID) for the benefit of developing countries. The views expressed are not necessarily those of DFID.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ICMR/MRC 1989

Methods	Randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: sealed envelopes Blinding: assessor only Inclusion of all randomized (enrolled) participants in the final analysis for primary outcomes: 1. Deformity: 73/130 (56%) at 3 years (73/94 available as x-rays technically inadequate or x-ray series incomplete for 21 participants); 65/130 (50%) at 5 years (15 participants not assessed for x-rays not being available on 0 or 60 months follow up) 2. Neurology: 68% (89/130) at 3 years; 62% (80/130) at 5 years; 5 participants excluded for neurological assessment (2 died of nontuberculous causes and 3 defaulted, all after 18 months) Length of follow up: 5 years, with assessment at 18 months, 3 years, and 5 years
Participants	Number (further details in Appendix 2): 201 enrolled and randomized 168 available for analysis at 3 years; losses to follow up due to no tuberculosis (3), refused surgery (2), considered unfit for the anaesthetic (1), considered unfit for surgery (3), no evidence of active spinal tuberculosis on radiographs (7), defaulted from 4 to 25 months (1), died of nontuberculous causes (6), operated at wrong level (1), missed considerable amount (> 6 weeks) of chemotherapy (9) 164 available for analysis at 5 years; losses to follow up due to reasons detailed above (33), excluded due to death of unrelated cause, default, or additional chemotherapy due to tuberculosis in other location (4; no details given) 156 available for analysis at 10 years; losses to follow up due to reasons detailed above during 0 to 5 years (37), and excluded for nontuberculous death (4) or default from follow up (4) Inclusion criteria: presence of clinical and radiographic evidence of tuberculosis of any vertebral body from the first thoracic to the first sacral, inclusive, that is excluding cervical and sacral disease; disease was active clinically and/or radiographically (radiographic active disease: (a) loss of the thin cortical outline and (b) rarefaction of the affected vertebral bodies); availability for observation over a period of 3 years Exclusion criteria: paraplegia or paraparesis severe enough to prevent walking; active tuberculosis in a lower limb requiring rest in bed; pulmonary tuberculosis of a type considered likely to complicate the management; history of previous antituberculosis chemotherapy for 12 months or more; serious nontuberculous disease likely to prejudice the response to treatment or its assessment; contraindication to the methods of the treatment under comparison
Interventions	1. Chemotherapy Adults (≥ 45 kg): daily streptomycin sulphate (1 g) by intramuscular injection for the first 3 months plus isoniazid (300 mg) and sodium p-amino salicylic acid (PAS) (10 g), both for 18 months Children (< 15 years) and adults (< 45 kg): daily streptomycin sulphate (20 mg/kg bodyweight) by intramuscular injection for the first 3 months plus isoniazid (6 mg/kg bodyweight; maximum 300 mg) and sodium PAS (0.2 mg/kg bodyweight; maximum 10 g), both for 18 months Participants randomized to this regimen or the same regimen without the initial 3 months of streptomycin 2. Chemotherapy plus debridement surgery Same chemotherapy regimen with debridement surgery: an operation to remove all necrotic and diseased tissue without reconstruction
Outcomes	1. Kyphosis angle 2. Neurological deficit 3. Bony fusion 4. Absence of spinal tuberculosis

ICMR/MRC 1989 (*Continued*)

	5. Deaths from any cause 6. Regained activity level 7. Change of allocated treatment
Notes	Location: Bulawayo, Rhodesia (now Zimbabwe) Date: 3-year follow up in 1974; 5-year follow up in 1978 The 5-year report contains information about a study from Hong Kong performed by the same group of investigators, the British Medical Research Council (MRC), with the same criteria; we excluded this part of the report from the analysis because participants were not randomized between chemotherapy or chemotherapy plus surgery

MRC 1974a

Methods	Randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: sealed envelopes Blinding: assessor only Inclusion of all randomized (enrolled) participants in the final analysis for primary outcomes: 1. Deformity: 39% (79/201) at 5 years; 34% (69/201) at 10 years; not available at 3 years; lumbar lesions excluded for deformity measurements, so total number less than 201, and, as a consequence, the percentages are higher than 39% and 34%, but exact figures cannot be reconstructed from article 2. Neurology: 80% (161/201) at 5 years; 78% (156/201) at 10 years; not available at 3 years Length of follow up: 10 years, with assessment at 18 months, and 3, 5, and 10 years
Participants	Number (further details in Appendix 2): 130 enrolled and randomized 94 available for analysis at 3 years, 36 lost to follow up due to no evidence on radiographs of tuberculosis (5), permanent default (6), excessive interruption (17), major drug change (3 toxicity, 1 brucellosis), death nontuberculous cause (3), admitted in error 1) 80 available for analysis at 5 years, 50 lost to follow up due to earlier exclusion (36 at 3 years), defaulted from follow up between 3 and 5 years (6), died of unrelated cause (3), not explained (5) Inclusion criteria: presence of clinical and radiographic evidence of tuberculosis of any vertebral body from the first thoracic to the first sacral, inclusive, that is excluding cervical and sacral disease; disease was active clinically and/or radiographically (radiographic active disease: (a) loss of the thin cortical outline and (b) rarefaction of the affected vertebral bodies); availability for observation over a period of 3 years Exclusion criteria: paraplegia or paraparesis severe enough to prevent walking; active tuberculosis in a lower limb requiring rest in bed; pulmonary tuberculosis of a type considered likely to complicate the management; a history of previous antituberculosis chemotherapy for 12 months or more; serious nontuberculous disease likely to prejudice the response to treatment or its assessment; a contraindication to the methods of the treatment under comparison
Interventions	1. Chemotherapy Isoniazid plus rifampicin (1 dose daily for 6 months) 2. Chemotherapy plus surgery Isoniazid plus rifampicin (1 dose daily for 6 months) with an operation consisting of debridement (removal of all necrotic and diseased tissue) and stabilization with a bone graft (reconstruction) Not included in review because it has a different chemotherapy regimen without a comparable surgical intervention group: 3. Chemotherapy Isoniazid plus rifampicin (1 dose daily for 9 months)

MRC 1974a (*Continued*)

Outcomes	1. Kyphosis angle 2. Neurological deficit 3. Bony fusion 4. Absence of spinal tuberculosis 5. Deaths from any cause 6. Regained activity level 7. Change of allocated treatment
Notes	Location: Madras, India Date: 3-year follow up in 1989; 5-year follow up in 1999; and 10-year follow up in 1999 The 5-year report also includes information from studies done in Hong Kong (all surgical) and Korea (all chemotherapy); we excluded these results from analysis because they did not randomize between chemotherapy alone and chemotherapy plus surgery

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Jain 2004	Not randomized
Loembe 1994	Not randomized
MRC 1973a	No surgical group
MRC 1973b	No surgical group
MRC 1974b	All participants had surgery
MRC 1976	No surgical group
MRC 1978a	All participants had surgery
MRC 1982	All participants had surgery
MRC 1985	No surgical group
MRC 1986	All participants had surgery
MRC 1993	No surgical group
MRC 1998	No randomization for conservative or surgical treatment: 2 locations, Korea (all chemotherapy without surgery) and Hong Kong (all chemotherapy plus surgery)
Rajasekaran 1998	No surgical group

(*Continued*)

Rajeswari 1997b	Not a randomized controlled trial, poor methodological quality, randomization method and concealment are unclear; study reports on 33 participants of whom the first 10 were not randomized but all operated because of participation in another trial (one of the included trials ICMR/MRC 1989); the other 23 patients were allocated to chemotherapy only, 4 were lost to follow up for various reasons; of the 19 included in the analysis 3 were operated for neurological deterioration
Seddon 1976	Description of several MRC studies, not a study itself
Upadhyay 1993	All participants had surgery
Upadhyay 1994a	All participants had surgery
Upadhyay 1994b	All participants had surgery
Upadhyay 1994c	All participants had surgery
Upadhyay 1996	All participants had surgery

DATA AND ANALYSES

Comparison 1. Chemotherapy plus surgery versus chemotherapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change of allocated treatment	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 At 18 months	2	262	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.27, 2.09]
1.2 At 3 years	2	262	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.25, 1.82]
1.3 At 5 years	2	244	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.25, 1.92]
1.4 At 10 years	1	156	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.28, 3.60]
2 Clinically significant increase in kyphosis angle	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Deterioration > 10 ° at 3 years	1	78	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.36, 2.16]
2.2 Deterioration > 10 ° at 5 years	2	144	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.54, 2.15]
3 Improvement in neurological deficit	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 At 18 months	2	23	Odds Ratio (M-H, Fixed, 95% CI)	3.18 [0.47, 21.67]
3.2 At 3 years	2	23	Odds Ratio (M-H, Fixed, 95% CI)	1.84 [0.33, 10.19]
3.3 At 5 years	2	20	Odds Ratio (M-H, Fixed, 95% CI)	2.14 [0.35, 13.13]
3.4 At 10 years	1	10	Odds Ratio (M-H, Fixed, 95% CI)	0.27 [0.01, 8.46]
4 Bony fusion	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 At 18 months	2	256	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.59, 1.59]
4.2 At 3 years	2	247	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.45, 1.27]
4.3 At 5 years	2	236	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.57, 2.00]
4.4 At 10 years	1	156	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [0.58, 2.81]
5 Absence of spinal tuberculosis	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 At 18 months	2	261	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.67, 2.05]
5.2 At 3 years	2	262	Odds Ratio (M-H, Fixed, 95% CI)	1.32 [0.58, 3.02]
5.3 At 5 years	2	244	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.36, 1.68]
5.4 At 10 years	1	156	Odds Ratio (M-H, Fixed, 95% CI)	1.67 [0.52, 5.35]
6 Deaths from any cause	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 At 18 months	2	262	Odds Ratio (M-H, Fixed, 95% CI)	2.65 [0.60, 11.64]
6.2 At 3 years	2	262	Odds Ratio (M-H, Fixed, 95% CI)	1.45 [0.42, 4.95]
7 Regained activity level	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 At 18 months	2	262	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.26, 1.66]
7.2 At 3 years	2	262	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.24, 1.50]
7.3 At 5 years	2	244	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.35, 1.85]
7.4 At 10 years	1	156	Odds Ratio (M-H, Fixed, 95% CI)	1.67 [0.52, 5.35]
8 Deterioration of bone loss	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 At 3 years	1	161	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.31, 1.09]
8.2 At 5 years	2	220	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.41, 1.29]

Analysis 1.1. Comparison 1 Chemotherapy plus surgery versus chemotherapy alone, Outcome 1 Change of allocated treatment.

Review: Routine surgery in addition to chemotherapy for treating spinal tuberculosis

Comparison: 1 Chemotherapy plus surgery versus chemotherapy alone

Outcome: 1 Change of allocated treatment

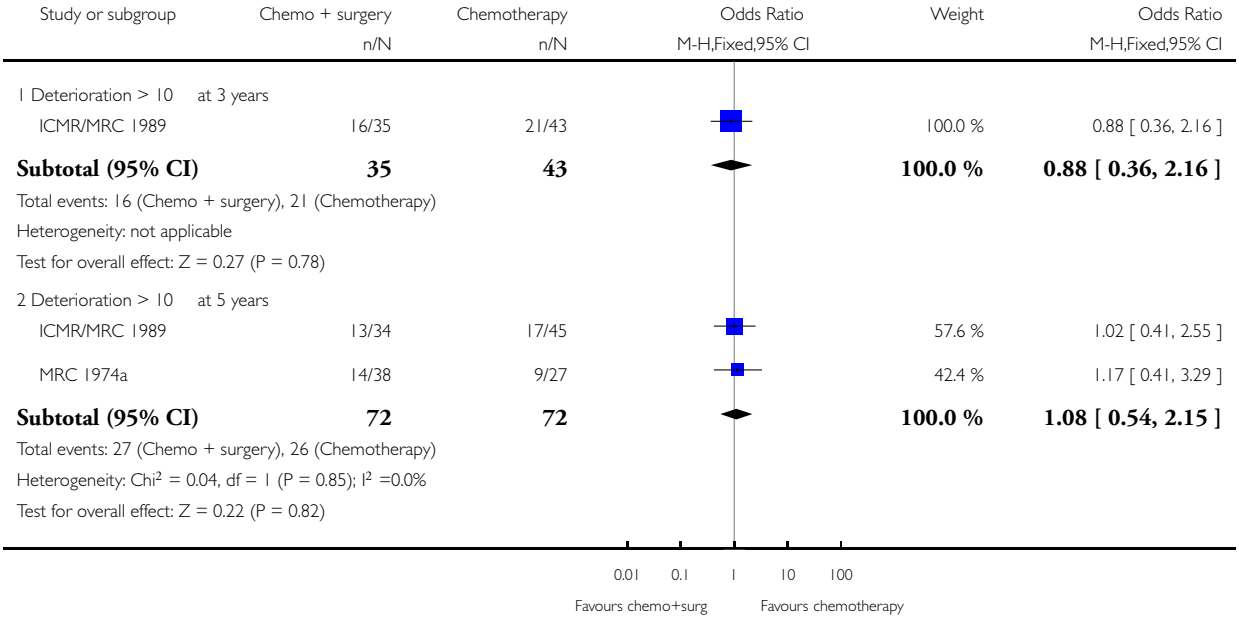
Study or subgroup	Chemo + surgery n/N	Chemotherapy n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 At 18 months					
ICMR/MRC 1989	5/85	5/83		55.4 %	0.98 [0.27, 3.50]
MRC 1974a	2/47	4/47		44.6 %	0.48 [0.08, 2.74]
Subtotal (95% CI)	**132**	**130**		**100.0 %**	**0.75 [0.27, 2.09]**
Total events: 7 (Chemo + surgery), 9 (Chemotherapy)					
Heterogeneity: Chi^2 = 0.42, df = 1 (P = 0.52); I^2 =0.0%					
Test for overall effect: Z = 0.55 (P = 0.59)					
2 At 3 years					
ICMR/MRC 1989	5/85	5/83		49.9 %	0.98 [0.27, 3.50]
MRC 1974a	2/47	5/47		50.1 %	0.37 [0.07, 2.03]
Subtotal (95% CI)	**132**	**130**		**100.0 %**	**0.67 [0.25, 1.82]**
Total events: 7 (Chemo + surgery), 10 (Chemotherapy)					
Heterogeneity: Chi^2 = 0.79, df = 1 (P = 0.37); I^2 =0.0%					
Test for overall effect: Z = 0.78 (P = 0.44)					
3 At 5 years					
ICMR/MRC 1989	5/82	5/82		52.2 %	1.00 [0.28, 3.59]
MRC 1974a	2/45	4/35		47.8 %	0.36 [0.06, 2.09]
Subtotal (95% CI)	**127**	**117**		**100.0 %**	**0.69 [0.25, 1.92]**
Total events: 7 (Chemo + surgery), 9 (Chemotherapy)					
Heterogeneity: Chi^2 = 0.85, df = 1 (P = 0.36); I^2 =0.0%					
Test for overall effect: Z = 0.70 (P = 0.48)					
4 At 10 years					
ICMR/MRC 1989	5/78	5/78		100.0 %	1.00 [0.28, 3.60]
Subtotal (95% CI)	**78**	**78**		**100.0 %**	**1.00 [0.28, 3.60]**
Total events: 5 (Chemo + surgery), 5 (Chemotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					

Analysis 1.2. Comparison 1 Chemotherapy plus surgery versus chemotherapy alone, Outcome 2 Clinically significant increase in kyphosis angle.

Review: Routine surgery in addition to chemotherapy for treating spinal tuberculosis

Comparison: 1 Chemotherapy plus surgery versus chemotherapy alone

Outcome: 2 Clinically significant increase in kyphosis angle

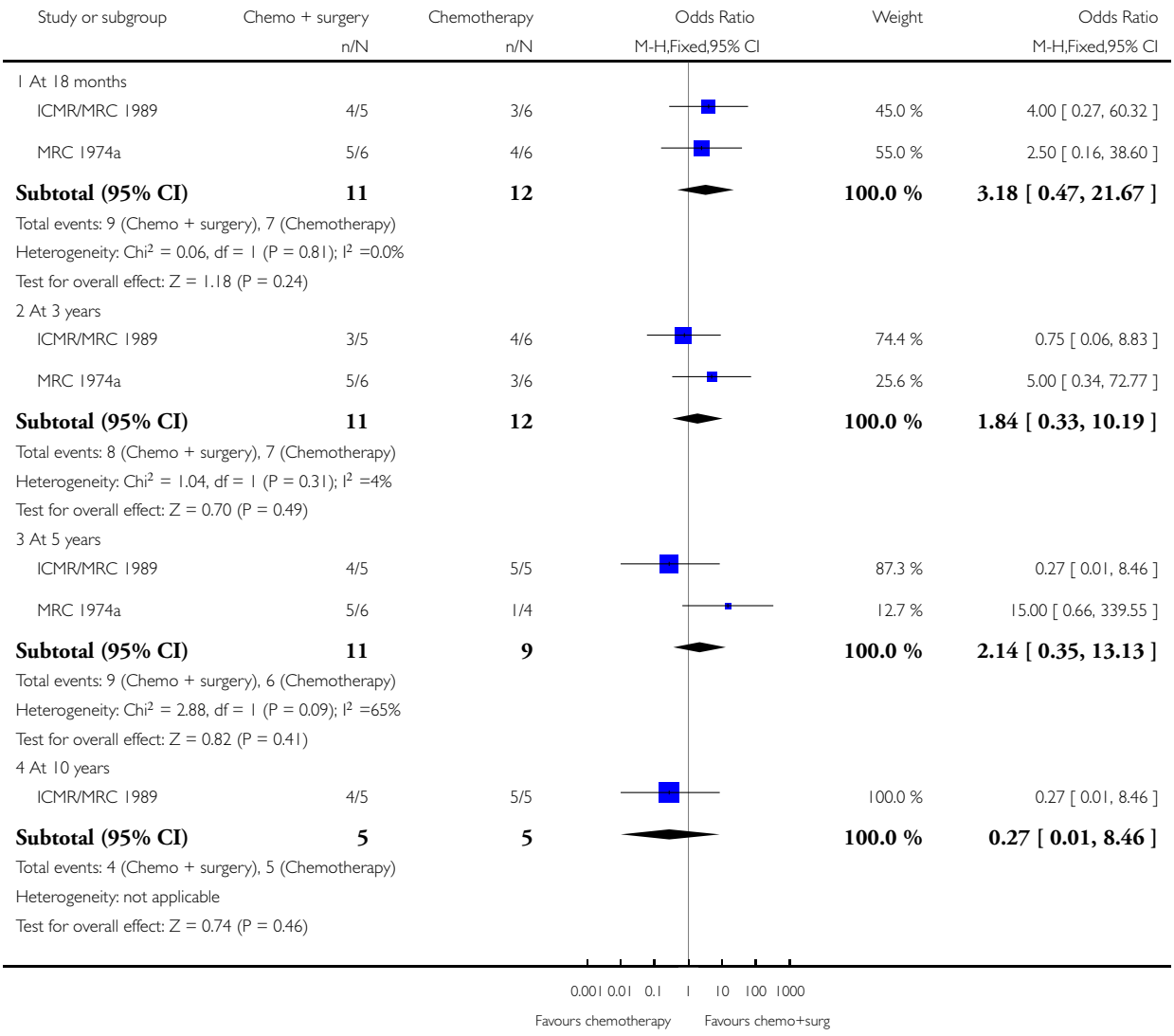


Analysis 1.3. Comparison 1 Chemotherapy plus surgery versus chemotherapy alone, Outcome 3 Improvement in neurological deficit.

Review: Routine surgery in addition to chemotherapy for treating spinal tuberculosis

Comparison: 1 Chemotherapy plus surgery versus chemotherapy alone

Outcome: 3 Improvement in neurological deficit

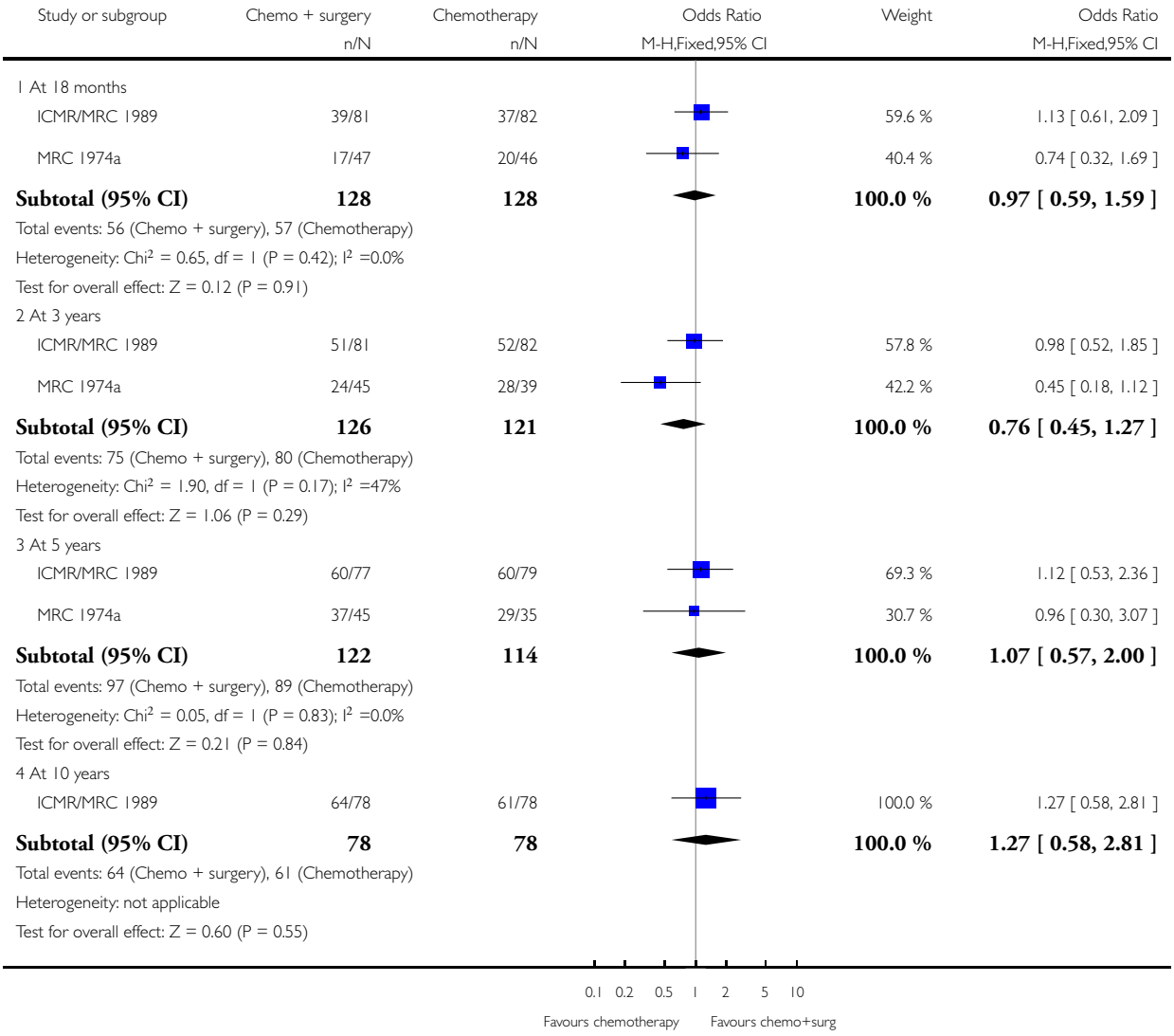


Analysis 1.4. Comparison 1 Chemotherapy plus surgery versus chemotherapy alone, Outcome 4 Bony fusion.

Review: Routine surgery in addition to chemotherapy for treating spinal tuberculosis

Comparison: 1 Chemotherapy plus surgery versus chemotherapy alone

Outcome: 4 Bony fusion



Analysis 1.5. Comparison 1 Chemotherapy plus surgery versus chemotherapy alone, Outcome 5 Absence of spinal tuberculosis.

Review: Routine surgery in addition to chemotherapy for treating spinal tuberculosis

Comparison: 1 Chemotherapy plus surgery versus chemotherapy alone

Outcome: 5 Absence of spinal tuberculosis

Study or subgroup	Chemo + surgery n/N	Chemotherapy n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 At 18 months					
ICMR/MRC 1989	57/85	53/83		77.8 %	1.15 [0.61, 2.18]
MRC 1974a	41/47	39/46		22.2 %	1.23 [0.38, 3.97]
Subtotal (95% CI)	**132**	**129**		**100.0 %**	**1.17 [0.67, 2.05]**
Total events: 98 (Chemo + surgery), 92 (Chemotherapy)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 0.55 (P = 0.58)					
2 At 3 years					
ICMR/MRC 1989	77/85	77/83		74.7 %	0.75 [0.25, 2.26]
MRC 1974a	44/47	39/47		25.3 %	3.01 [0.75, 12.14]
Subtotal (95% CI)	**132**	**130**		**100.0 %**	**1.32 [0.58, 3.02]**
Total events: 121 (Chemo + surgery), 116 (Chemotherapy)					
Heterogeneity: Chi^2 = 2.35, df = 1 (P = 0.13); I^2 =57%					
Test for overall effect: Z = 0.66 (P = 0.51)					
3 At 5 years					
ICMR/MRC 1989	72/82	75/82		61.2 %	0.67 [0.24, 1.86]
MRC 1974a	37/45	29/35		38.8 %	0.96 [0.30, 3.07]
Subtotal (95% CI)	**127**	**117**		**100.0 %**	**0.78 [0.36, 1.68]**
Total events: 109 (Chemo + surgery), 104 (Chemotherapy)					
Heterogeneity: Chi^2 = 0.20, df = 1 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 0.63 (P = 0.53)					
4 At 10 years					
ICMR/MRC 1989	73/78	70/78		100.0 %	1.67 [0.52, 5.35]
Subtotal (95% CI)	**78**	**78**		**100.0 %**	**1.67 [0.52, 5.35]**
Total events: 73 (Chemo + surgery), 70 (Chemotherapy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.86 (P = 0.39)					

Analysis 1.6. Comparison 1 Chemotherapy plus surgery versus chemotherapy alone, Outcome 6 Deaths from any cause.

Review: Routine surgery in addition to chemotherapy for treating spinal tuberculosis

Comparison: 1 Chemotherapy plus surgery versus chemotherapy alone

Outcome: 6 Deaths from any cause

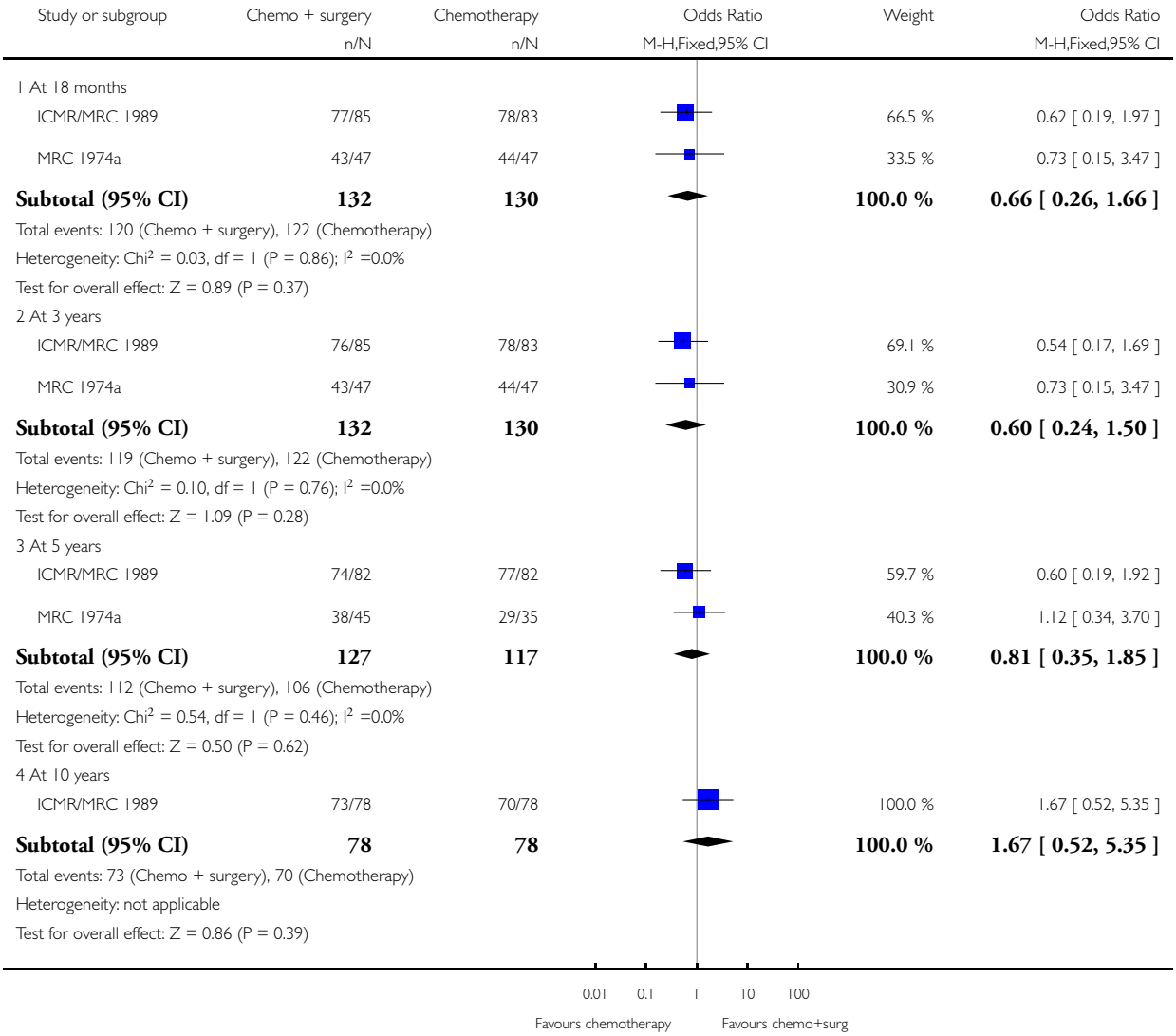
Study or subgroup	Chemo + surgery n/N	Chemotherapy n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 At 18 months					
ICMR/MRC 1989	4/85	0/83		20.0 %	9.22 [0.49, 174.01]
MRC 1974a	2/47	2/47		80.0 %	1.00 [0.13, 7.41]
Subtotal (95% CI)	**132**	**130**		**100.0 %**	**2.65 [0.60, 11.64]**
Total events: 6 (Chemo + surgery), 2 (Chemotherapy)					
Heterogeneity: Chi^2 = 1.60, df = 1 (P = 0.21); I^2 =38%					
Test for overall effect: Z = 1.29 (P = 0.20)					
2 At 3 years					
ICMR/MRC 1989	2/47	4/47		88.9 %	0.48 [0.08, 2.74]
MRC 1974a	4/85	0/83		11.1 %	9.22 [0.49, 174.01]
Subtotal (95% CI)	**132**	**130**		**100.0 %**	**1.45 [0.42, 4.95]**
Total events: 6 (Chemo + surgery), 4 (Chemotherapy)					
Heterogeneity: Chi^2 = 3.07, df = 1 (P = 0.08); I^2 =67%					
Test for overall effect: Z = 0.59 (P = 0.55)					

Analysis 1.7. Comparison 1 Chemotherapy plus surgery versus chemotherapy alone, Outcome 7 Regained activity level.

Review: Routine surgery in addition to chemotherapy for treating spinal tuberculosis

Comparison: 1 Chemotherapy plus surgery versus chemotherapy alone

Outcome: 7 Regained activity level

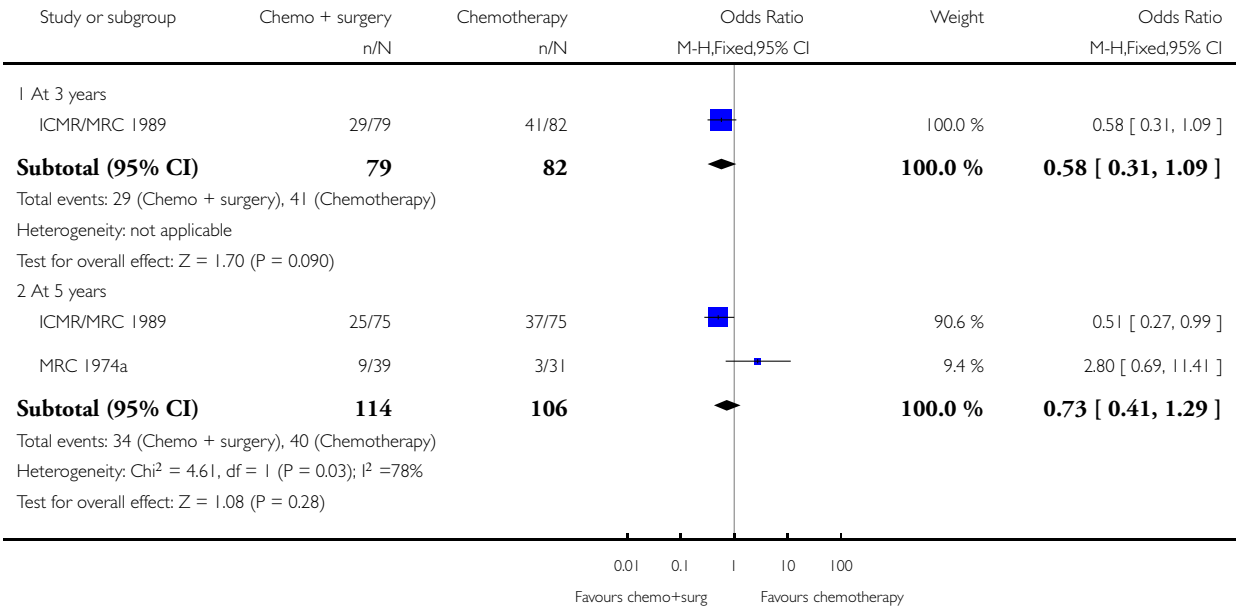


Analysis 1.8. Comparison 1 Chemotherapy plus surgery versus chemotherapy alone, Outcome 8 Deterioration of bone loss.

Review: Routine surgery in addition to chemotherapy for treating spinal tuberculosis

Comparison: 1 Chemotherapy plus surgery versus chemotherapy alone

Outcome: 8 Deterioration of bone loss



APPENDICES

Appendix 1. Search methods: detailed search strategies

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	tuberculosis	TUBERCULOSIS SPINAL	TUBERCULOSIS, SPINAL	tuberculosis spondylitis	spinal tuberculosis
2	spine	Pott[a] disease	spinal tuberculosis	TUBERCULOUS SPONDYLITIS	TUBERCU-LOUS SPONDYLITIS tuberculous spondylitis
3	-	1 or 2	tuberculous spondylitis	spinal tuberculosis	Pott's disease

(*Continued*)

4	-	-	spinal TB	spinal TB	1 or 2 or 3
5	-	-	Pott's disease	vertebral tuberculosis	-
6	-	-	Pott's paraplegia	Pott's disease	-
7	-	-	1 or 2 or 3 or 4 or 5 or 6	1 or 2 or 3 or 4 or 5 or 6	-

[a] Cochrane Infectious Diseases Group Specialized Register.
[b] Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2005); upper case: MeSH or EMTREE heading; lower case: free text term.

Appendix 2. Characteristics of included participants

Characteristic	MRC 1974a	ICMR/MRC 1989
Number enrolled	130	201
Number available at follow up	3 years: 94 (47 in each arm) 5 years: 80 (45 in surgical arm, and 35 in chemotherapy alone arm) (some data available at 18 months)	3 years: 168 (85 in surgical arm, and 83 in chemotherapy alone arm) 5 years: 164 (82 in each arm) 10 years: 156 (78 in each arm) (some data available at 18 months)
Age	Of the 94 people available for analysis at 3 years: 16 were < 15 years and 78 ≥ 15 years; age range not given	Of the 168 people available for analysis at 3 years: 63 were < 15 years; 105 ≥ 15 years; age range not given
Gender	Of the 94 people available for analysis at 3 years 52 were male and 42 female	Not given
Number vertebrae involved	1 or 2 in 70 participants > 2 in 24 participants	1 or 2 in 115 participants > 2 in 53 participants
Location of lesions	Thoracic (39 participants) Thoracolumbar (10 participants) Lumbar (45 participants)	Thoracic or thoracolumbar (84 participants) Lumbar or lumbosacral (84 participants)
Kyphosis angle at entry	27° (40 surgical group participants) 24° (33 chemotherapy group participants) (standard deviation not provided)	Only provided for thoracic or thoracolumbar localization: 29° (mean in the surgical group) 29° (mean in the chemotherapy group) (standard deviation not provided) > 20° in 66 of 84 patients with thoracic or thoracolumbar localizations

(*Continued*)

Mean total bone loss at start of treatment	0.8 U (treatment group) 0.7 U (control group) (standard deviation not provided)	0.8 U (treatment group) 1.0 U (control group) (standard deviation not provided)
Neurological deficit on entry	12/94 participants 12 had incomplete paraplegia but were able to walk (inclusion criterion for this trial)	11/168 participants 11 had incomplete paraplegia but were able to walk (inclusion criterion for this trial)

Appendix 3. Risk of bias (methodological quality) of included studies[a]

Trial	Allocation sequence generation	Allocation concealment	Inclusion[b]
MRC 1974a	Unclear	Adequate	Kyphosis angle and neurology: inadequate at 3 and 5 years follow up
ICMR/MRC 1989	Unclear	Adequate	Kyphosis angle: inadequate at 3, 5, and 10 years follow up Neurology: adequate at 3 and 5 years follow up, and inadequate at 10 years follow up

[a] Details in the 'Characteristics of included studies'.
[b] Inclusion of all randomized (enrolled) participants in the analysis for primary outcomes.

Appendix 4. Reasons for changing allocated treatment

Trial	Intervention	No. participants	Reason for change	Details
MRC 1974a	Chemotherapy plus surgery	2	Additional treatment needed	Received extra chemotherapy for persistent sinus
	Chemotherapy	3	Additional treatment needed	Received extra chemotherapy for progressive neurological deficit
	Chemotherapy	2	Randomization broken	Needed decompression operation because of progressive neurological deficit
ICMR/MRC 1989	Chemotherapy plus surgery	1	Additional treatment needed	Bone graft displaced posteriorly and a second operation needed to remove the graft

(*Continued*)

	Chemotherapy plus surgery	1	Additional treatment needed	Developed myelopathy with complete paralysis immediately postoperative for which additional chemotherapy was added in third month
	Chemotherapy plus surgery	1	Additional treatment needed	Developed a sinus and graft infection that needed a second operation to remove graft
	Chemotherapy plus surgery	2	Randomization broken	Problem with exposure of lesion during operation, which had to be abandoned; both received chemotherapy as allocated
	Chemotherapy	3	Randomization broken	Needed decompression operation because of progressive neurological deficit
	Chemotherapy	2	Randomization broken	Developed abscesses that were treated with additional chemotherapy

Appendix 5. Mean kyphosis angle (degrees)

	MRC 1974a		ICMR/MRC 1989	
	Chemotherapy plus surgery	**Chemotherapy alone**	**Chemotherapy plus surgery**	**Chemotherapy alone**
Lesions	T1 to S1	T1 to S1	T1 to L2	T1 to L2
Angle at start	27°	24°	29°	29°
Angle at 18 months	40°	30°	41°	41°
Angle at 3 years	40°	32°	41°	42°
Angle at 5 years	39°	30°	37°	40°
Angle at 10 years	-	-	41°	47°

(*Continued*)

Increase in angle at 18 months	13° (40 participants)	6° (33 participants)	12° (34 participants)	12° (42 participants)
Increase in angle at 3 years	13° (40 participants)	8° (33 participants)	12° (34 participants)	13° (42 participants)
Increase in angle at 5 years	12° (34 participants)	6° (24 participants)	8° (34 participants)	11° (45 participants)
Increase in angle at 10 years	-	-	12° (28 participants)	18° (41 participants)

Appendix 6. Deaths from any cause

Trial	Time of death	Cause of death	Chemotherapy		Group not provided
			Plus surgery	Alone	
MRC 1974a	3 months	Unknown, 60 years, 5 weeks after decompression surgery for progressive neurological deficit (change of allocated treatment)	-	1	-
	3 months	Cerebral haemorrhage	1	-	-
	9 months	Pneumonia and dysentery	1	-	-
	11 months	Undiagnosed acute illness	-	1	-
	23 months	Heart failure in 24 year old	-	1	-
	31 months	Sudden death from unknown cause, 53 years	-	1	-
	3 to 5 years	Stomach cancer	1	-	-
	3 to 5 years	Unknown	-	1	-

(*Continued*)

	3 to 5 years	Heart failure	-	1	-
ICMR/MRC 1989	1 month	Died < 24 h from disseminated coagulation disorder, woman 25 years	1	-	-
	1 month	Died < 24 h from acute dilatation of the stomach, man 60 years	1	-	-
	1 month	Died from secondary haemorrhage four weeks postoperatively, woman 18 years	1	-	-
	5 months	Died in the 5th month of dyspnoea supposedly from a pulmonary embolism, woman 35 years	-	-	-
	< 1 year	Myocardial infarction	-	-	1
	< 1 year	Burn wounds	-	-	1
	< 1 year	Malignant disease	-	-	1
	< 1 year	Fall from height	-	-	1
	1 to 2 years	Encephalitis	-	-	1
	1 to 2 years	Unknown	-	-	1
	2 to 3 years	Viral infection	-	-	1
	2 to 3 years	Pyrexia of unknown origin	-	-	1
	3 to 5 years	Unknown, nontuberculous	-	-	5
	5 to 10 years	Unknown, nontuberculous	2	2	-

Appendix 7. Bone loss (U)

Trial	Intervention	Fraction loss: start	Deterioration			Total bone loss: 5 years
			18 months	3 years	5 years	
MRC 1974a	Chemotherapy plus surgery	0.8	0.2	0.3	0.2	1.0
	Chemotherapy	0.7	0.1	0.1	0.0	0.7
ICMR/MRC 1989	Chemotherapy plus surgery	0.8	0.3	0.3	0.3	1.1
	Chemotherapy	0.95	0.4	0.5	0.5	1.45

Appendix 8. Adverse events

Adverse event	Trial	Chemotherapy	
		Plus surgery	Alone
Operated on the wrong level (excision of healthy bone instead of diseased bone)	ICMR/MRC 1989	1	0
Cases of hepatitis	"	17	11
Graft failure by breakage or displacement, in all these patients the graft spanned more than 3 disc spaces (at 10 year follow up)	"	7	0

WHAT'S NEW

Last assessed as up-to-date: 22 October 2007.

Date	Event	Description
24 April 2013	New search has been performed	New search conducted 28 November 2012; no new studies found.

HISTORY

Protocol first published: Issue 4, 2003

Review first published: Issue 1, 2006

Date	Event	Description
15 February 2010	New search has been performed	new search conducted; no new studies found
5 November 2008	Amended	Converted to new review format with minor editing.
23 May 2006	Amended	2006, Issue 3: Corrected an error in the 'Characteristics of included studies' where the data for 'Participants' were entered in the wrong columns

CONTRIBUTIONS OF AUTHORS

Paul Jutte took the lead in preparing the review and is the guarantor. Joke van Loenhout-Rooyackers helped design the study, write the background, determine the outcome measures, and also cross checked all data.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department for International Development (DFID), UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2006, Issue 1 (first version of review): We added a new outcome, bone loss, because both trials included data on this. In our protocol, we had stated that we would consider outcomes reported between 12 and 24 months because we did not expect to find trials that followed participants for a longer period. Both included trials follow the participants for much longer, so we decided to report on all outcomes reported. We modified one of the subgroup group analyses so that the cut-off age for children became 15 years old instead of 18 years old (as stated in the protocol) because 15 years old is generally when growth stops and both trials used this age. We were however unable to use some methods described in the protocol because there were too few included trials.

INDEX TERMS

Medical Subject Headings (MeSH)

Aminosalicylic Acid [therapeutic use]; Antitubercular Agents [*therapeutic use]; Combined Modality Therapy [methods]; Isoniazid [therapeutic use]; Kyphosis [etiology]; Randomized Controlled Trials as Topic; Rifampin [therapeutic use]; Streptomycin [therapeutic use]; Tuberculosis, Spinal [complications; *drug therapy; *surgery]

MeSH check words

Humans